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(54) Title: A BIOMATERIAL AND BONE IMPLANT FOR BONE REPAIR AND REPLACEMENT

(57) Abstract

This invention relates to a biomaterial useful in bone repair and replacement, and to implants for cranofacial, orthopaedic, and especially dental applications. The implants have a unique geometric configuration, their surfaces defining concavities having a shape and dimensions which induce or enhance the rate and/or amount of bone growth at the implant site. The biomaterial preferably has a specific porous configuration and the implant may be at least coated with such a biomaterial of hydroxyapatite, for example.

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Title: A biomaterial and bone implant for bone repair and replacement.

This invention relates to a biomaterial useful in bone repair and replacement, and to implants for craniofacial, orthopaedic, and especially dental applications.

Successful osteointegration of implants for dental, craniofacial and orthopaedic applications is a problem central to oral and skeletal rehabilitation.

Conventional treatment of bone defects requires the use of either organic (bone derived) or inorganic (man made) biomaterials for successful restoration of form and function, preferably biomaterials with interconnected porous spaces across the substratum of the biomaterial. This allows bone growth into the porous spaces of the biomaterial, securing its incorporation and osteointegration with the surrounding viable bone at the margins of the bone defect. Porous biomaterials which allow bone growth thus into their porous spaces are defined as osteoconductive biomaterials.

The necessity of having viable bone in direct contact with the porous biomaterial to ensure adequate bone ingrowth via osteoconduction is, however, a limiting factor particularly in large bony defects, since the depth of bone penetration within the porous spaces may be confined to the peripheral regions of

the implant only. Furthermore, a perfect fit of an implant, designed for orthopaedic and dental applications either for bone repair or replacement, within a bone defect is often technically difficult to achieve, since it is not always possible to prepare the bone margins precisely so as to provide a perfect fit to the implants. Thus, in spite of technological advances in implant design and fabrication, osteointegration often does not occur or is not maintained along the entire implant surface.

Thus for several applications, it would be preferred for bone to grow more rapidly into the porous spaces and, further, for bone to form independently of the surrounding viable bone, within the biomaterial. The formation of bone within a porous biomaterial independent of the presence of viable bone (when for example the biomaterial is implanted in extraskeletal sites) is defined as osteoinduction. One approach for preparing an osteoinductive material is to adsorb onto its surfaces exogenous growth and morphogenetic factors which are capable of inducing differentiation of bone within the porous spaces of the biomaterial. These molecular initiators of bone formation are collectively named bone morphogenetic proteins (BMPs).

This, however, requires the complexing, onto the biomaterial, of either native BMPs (isolated and purified from organic bone matrix - in particular bovine bone) or recombinant human BMPs, with the accompanying disadvantages of a limited shelf life and possible adverse systemic effects. A preferred alternative would be a biomaterial which is capable of spontaneously initiating bone formation within the porous spaces independent of the presence of viable bone at its interfaces.

The Applicant is aware of previous studies involving the calcium phosphate ceramic called hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] obtained after hydrothermal chemical exchange with phosphate converting the original calcium carbonate exoskeletal microstructure of the scleractinian reef-building coral of the genus Goniopora [1] into an inorganic replica of hydroxyapatite [2-4]. Conversion to hydroxyapatite is monitored by X-ray diffraction pattern, showing that hydroxyapatite replicas consist of ± 90% hydroxyapatite and 10% tricalcium phosphate. Previous studies by one of the inventors, Dr Ripamonti, using coral-derived hydroxyapatite introduced the concept that the shape and configuration (hereinafter referred to as "the geometry") of the hydroxyapatite implant regulate the initiation of bone formation in vivo [6]. These

studies showed that in extraskeletal sites of rodents, bone did not form in implants of granular hydroxyapatite, even when pre-treated with bone morphogenetic proteins (BMPs) (which initiate bone differentiation in vivo), while bone formation was observed in porous blocks of hydroxyapatite [5-8]. As part of the research into the subject of spontaneous bone growth and, in particular, the optimum conditions for initiating bone growth, extraskeletal implantation of different forms of hydroxyapatite into primates indicated that the geometry of the hydroxyapatite indeed is important and indeed might even be critical for bone induction to occur [5,7,8]. When implanted intramuscularly in baboons, granular hydroxyapatite implants did not induce the differentiation of bone, while reproducible bone differentiation was observed in porous blocks of hydroxyapatite with identical surface characteristics [5,7,8].

Thus it appeared from said inventor's studies that a critical difference between geometries is the presence of convexities in granular hydroxyapatite and, conversely, the presence of concavities (of the porous spaces) in the blocks of hydroxyapatite.

Accordingly it is an object of this invention to provide implants for bone repair and bone replacement having a defined macrostructure and especially a

defined geometric configuration of the implant surface, i.e. implants with geometric osteoinductive configurations.

It is another object of this invention to provide a biomaterial for bone replacement which is capable of spontaneous initiation of bone formation, i.e. a biomaterial with intrinsic osteoinductive activity.

It is another object of this invention to provide sintered porous ceramic biomaterials and methods for their manufacture derived from synthetic hydroxyapatite particles as starting material.

It is a further object of this invention to provide sintered ceramic biomaterials capable of osteoconduction when implanted into a bone defect.

It is a further object of this invention to provide sintered porous ceramic biomaterials for bone replacement having a defined porous macrostructure and especially a defined geometric configuration of the porous structure (osteoinductive configuration).

It is a further object of this invention to enhance the extent of bone formation and/or bone growth by pre-treatment of the porous sintered hydroxyapatite with liquid etchants.

It is yet a further object of this invention to provide porous sintered ceramic biomaterials which provide an optimal substratum for adsorption of growth and morphogenetic factors, including, but not limited to BMPs.

It is a still further object of this invention to provide a composite of porous ceramic and native or recombinant human BMPs for the rapid initiation of bone formation within the porous spaces of the implant.

A further, important object of this invention is to provide a bone implant for orthopaedic, craniofacial, and particularly dental applications.

How the objectives of this invention are achieved will become apparent in the light of the following disclosure.

Whilst restoration of bone defects may be sought by insertion at the site of the bone defect of porous osteoconductive biomaterials or implants, in several instances treatment requires the insertion of solid prostheses that substitute for a part of the skeleton, as commonly done for femoral and knee replacement (for example, hip and knee prosthesis).

Similarly, dental implants (usually of titanium with or without hydroxyapatite coating) are used as surrogates of tooth roots after implantation in edentulous jaws. Both porous biomaterial implants and solid prosthetic implants for orthopaedic, craniofacial and dental applications need to integrate with the host viable bone for successful osteointegration. It is common knowledge that osteointegration may not occur or is not maintained along the entire surface of solid prosthetic implants for orthopaedic, craniofacial and dental applications. Excluding failures attributable to implant micromotion and infection, lack of optimal osteointegration along solid prosthetic implants may be due to inadequate consideration of the geometric configuration of the implant surface.

Thus, the importance of geometry of an implant for bone repair and replacement may not be limited to the internal porous configuration (as in the case of porous biomaterial implants) but also to the external design of solid prostheses to be used for orthopaedic and dental applications.

The present invention is the innovative application of the results of the inventors' research and experimentation into the importance of the geometric configuration of a material for use in bone

repair and replacement, in the form of a manufactured article having a unique outer implant surface, and in the form of a biomaterial having both a unique implant surface and a unique porous configuration, for use in particular embodiments of the article, and that is capable of inducing the spontaneous initiation of bone formation even if not in direct contact with viable bone.

According to the invention, broadly, there is provided a bone implant for implanting into a subject at a site where bone growth is required, said implant comprising a body with an outer surface which defines dents which are selected, according to their shape and dimensions, for their ability to induce or to enhance the rate and/or amount of bone growth at the site.

The dents may be in the form of concavities having a diameter in the region of about 200μm to about 3000μm, more preferably 1600μm, and with a depth in the region of about 200μm to about 3000μm, more preferably about 800μm.

In the following disclosure, it will become apparent that the osteoinductive geometric configuration can be imparted to a porous biomaterial implant for applications in bone repair (i.e., by fabricating a porous biomaterial with specific

geometry of the porous spaces within and on the outer surface of the implant) as well as solid prosthetic implants in which the specific geometric configurations are imparted only to the external surface of the implant. By virtue of the preparation of osteoinductive geometric configurations, both biomaterial implants are endowed with intrinsic osteoinductive activity.

For the purpose of the porous biomaterial implant with osteoinductive geometric configuration, according to the invention, there is provided a method of preparing a biomaterial which can be used for at least part of a bone implant to be implanted into a patient at a site where bone growth is required, which method includes preparing the biomaterial of a sintered ceramic with an interconnected porous configuration which includes concavities having such shapes and dimensions as impart to the biomaterial the ability to induce or enhance the rate and/or amount of bone growth at the site.

The biomaterial may be made by a range of ceramic processing techniques including, but not limited to a fugitive phase method or by a sponge impregnation method.

If the fugitive phase method is used, then it involves selecting or manufacturing stearic acid beads of a suitable size, mixing a ceramic powder with the stearic acid beads, compacting the resulting mixture to form a compact, and sintering the compact.

A typical fugitive phase method for making the biomaterial of the invention is the following.

Stearic acid is obtained from SMM Chemicals under product number 8224 and stearic acid beads are manufactured to approximately the required size, typically 1-2mm diameter. The yield is then sieved to obtain a narrow distribution around the required size. Hydroxyapatite powder obtained from Merck S.A. under product number 2196 and the classified stearic acid beads are mixed by tumbling without additives in a proportion of 70% beads by mass. The resulting dry mixture is loaded into a press mould, sealed, and cold isostatically pressed at a pressure of 200 MPa. The green compact thus produced is machined if necessary. The green compact is placed on platinum foil and sintered according to the following program:

Segment	1	2	3	4	5
Temperature (°C)	25	300	1200	1200	25
Time (hrs)	0	6	6	1	6

If the sponge impregnation method is used then it involves attaching a layer of synthetic hydroxyapatite to the surfaces of a polyurethane foam material having continuous and interconnecting pores. This impregnated foam is then thermally treated to form a reticulated ceramic with three-dimensional continuous pores. More particularly this method includes

(a) selecting an organic resin with a three-dimensional network structure which is a negative replica of the desired configuration of the biomaterial,

(b) impregnating a slurry of a ceramic into the organic resin,

(c) drying the slurry, and

(d) removing the organic resin.

The porous sintered hydroxyapatite artefact fabricated using either of the methods described above will consist of a framework of hydroxyapatite delineating porous spaces formed by the coalescence of repetitive sequence of concavities.

The irregular spheroid shape of the resin and their interconnections provide a three dimensional foamy-like network, and the resulting hydroxyapatite artefact defines porous spaces having a plurality of concavities often separated by convexities, ie the hydroxyapatite is a replica of the organic resin.

Variable dimensions of the concavities which make the porous spaces after sintering the hydroxyapatite slurry can be obtained by using polyurethane foams of different dimensions increasing or decreasing the dimensions of the starting resin material, it is possible to obtain porous spaces made of larger or smaller concavities when sintering the hydroxyapatite slurry.

The optimum dimensions of the concavities imparting the specific osteoinductive geometric configuration to the porous biomaterial as determined by the inventors, is as follows:

The inner geometry of the biomaterial is characterised by pores which are substantially spherical in shape and in the region of 300μm to 3000μm in diameter, preferably about 1600μm.

It is important to point out that the substantial spheroidal shape of the porous spaces is due to the apposition, within the inner part of the porous biomaterial, of single concavities specifically fabricated by both fugitive and impregnation methods described above.

The specific geometric configuration of the biomaterial is also imparted at the outer surface of the porous biomaterial.

Thus, at the outer surface of the biomaterial, the osteoinductive geometric configurations are concavities with a maximum diameter in the region of about 200μm to about 3000μm, more preferably 1600μm, and with a maximum depth in the region of about 200μm to about 3000μm, more preferably about 800μm.

Thus according to the invention there is provided a biomaterial implant for bone repair which is capable of spontaneous induction of bone both within the inner porous spaces, and the concavities prepared on the outer surface of the biomaterial implant. The ability to induce bone formation in the concavities of the outer surface is advantageous, since this will enhance the rate of osteointegration with the surrounding viable bone when implanted into a patient at a site where bone growth is required.

The invention extends to a method of inducing and enhancing the rate and amount of bone growth in a patient, in a site where bone growth is desired, which includes

selecting a porous biomaterial implant having an appropriate overall shape and size for accommodation at the site of a bone defect, and comprising a porous framework, preferably of sintered hydroxyapatite, within porous spaces and

outer surface concavities having a diameter of about 200μm to about 3000μm and a depth of about 200μm to about 1600μm, and

placing the porous biomaterial implant in the patient at the site of a bone defect where bone formation and growth is required.

Where the porous biomaterial implant is made of sintered hydroxyapatite, the method may include treating the outer and inner surfaces of the porous implant with etchants, and may further include adsorbing bone morphogenetic proteins onto the porous spaces of the implant, before placing the implant in the site where bone growth is required. In this case, there is potentiation of the bone inductive activity by the exogenous application of BMPs.

A preferred method of treating the biomaterial is to wet the sintered hydroxyapatite of which it is made, by pipetting suitable amounts of 5mM hydrochloric acid (preferably about 300μl per 1000μg of sintered hydroxyapatite) onto and into the hydroxyapatite substratum. In this case the biomaterial of the invention not only induces but also enhances the rate and amount of bone formation and growth.

For the purpose of the solid implant with osteoinductive geometric configurations for dental, craniofacial and orthopaedic applications, according to the invention, there is provided a solid implant for implantation into a patient at a site where bone replacement is required, said implant comprising a body with an outer surface with specific geometric configurations, which are selected, according to their ability to induce the spontaneous initiation of bone and to enhance the rate and the amount of bone at the site of implantation.

The optimum geometric configuration of the outer surface of the solid implant as determined by the inventors is as follows:

At the outer surface of the solid biomaterial implant, the preferred geometric configuration are concavities with a maximum diameter in the region of about 200μm to about 3000μm, more preferably 1600μm, and with a maximum depth in the region of about 200μm to about 3000μm more preferably about 800μm. The regions of the outer surfaces at the respective peripheries of the concavities, may be rounded, and in a preferred embodiment of the biomaterial according to the invention, the outer surface generally does not have any sharp edges and the indentations are spaced apart from one another by a distance of

about 500μm to about 3000μm preferably about 2000μm.

The invention extends to a method of inducing or enhancing the rate and/or amount of bone growth in a patient, in a site where bone replacement is desired, which includes

selecting a solid implant having an appropriate overall shape and size for accommodation in the site, and comprising a body with an outer surface which defines concavities having a diameter of about 200μm to about 3000μm and a depth of about 200μm to about 1600μm and

placing the implant in the patient in the site where bone replacement and growth is required.

In a preferred embodiment of an implant according to the invention, the solid implant is preferably of sintered hydroxyapatite or other ceramics such as zirconia and alumina.

According to the invention there is provided a solid implant made of sintered hydroxyapatite with specific geometric configuration which are selected, according to their shape and dimensions, for their ability to induce the spontaneous initiation of bone

and to enhance the rate and/or amount of bone at the site of implantation into a patient.

The manufacture of solid implants of hydroxyapatite with specific concavities prepared on the outer surface involves mixing of ceramic powder (such as hydroxyapatite) with binder, pressing the compacts using a die and pistons with specific concavities and sintering the said compacts.

A typical process includes the following: Polyethylene glycol 1000 binder, (Merck product number 807468), is added at 15% by mass to hydroxyapatite powder by dissolving the binder in ethanol, adding the hydroxyapatite and subsequently evaporating the ethanol whilst mixing.

The powder is pressed at a pressure of 5-20 MPa in a die between two pistons, lubricated with a solution of stearic acid in ethanol. Damage of the compact during separation from the pistons was minimised by placing double sheets of thin polyethylene sheets between the powder and pistons before pressing. The pistons contain hemispherical protrusions of 1000μm and 2000μm diameter, respectively, produced by drilling holes and brazing 1000μm and 2000μm diameter

steel spheres to a depth of 1 radius in the flat piston surfaces. Compacts of hydroxyapatites of any shape with concavities on the outer surface of 1000μm and 2000μm respectively, are thus produced on the flat surfaces. The green compacts are then placed on platinum foil covered and sintered.

If the hydroxyapatite used for the preparation of the compacts is hydroxyapatite powder from Merck S.A. (product number 2196) then compacts are sintered according to the following program:

Segment	1	2	3	4	5
Temperature (°C)	50	400	1150	1150	20
Time (hrs)	1	10	4	1	4

Furthermore, the solid implant of sintered hydroxyapatite may have BMPs adsorbed thereon, to further potentiate and/or accelerate induction of bone formation.

Whilst a preferred method for preparing such solid implants, as described above for dental and orthopaedic applications is using sintered hydroxyapatite or other ceramics such as zirconia and alumina, it is also possible to prepare according to

the invention solid implants made of metals (preferably bio-tolerant such as titanium).

In such cases of solid implants made of titanium or other bio-tolerant metals, the implant has an outer coating of an additional biomaterial over the outer surface concavities as described above. The biomaterial may be hydroxyapatite, or such other biomaterial as may aid osteointegration of the implant in use. Such a coating will be bio-active, e.g. hydroxyapatite (or derivatives such as fluoroapatite), BIOGLASS®, CERAVITAL®; bio-inert, e.g. alumina, silicon nitride, pyrolytic carbon; bio-tolerant, e.g. polytetrafluoroethylene (PTFE), polymethyl methacrylate (PMMA), or bio-resorbable, e.g. polyglycolic acid (DEXON S®), 90% polyglycolic acid/polylactic acid (VICRYL®), poly(hydroxybutyrate)-poly)hydroxyvalerate) (PHB-PHV), tricalcium phosphate. Typically, a calcium phosphate ceramic, such as hydroxyapatite is applied to the outer surface of the implant body. The thickness of the coating applied to the outer body of the solid implant may be in the region of about 50μm to about 400μm or more, preferably in the region of 60μm to 120μm.

Furthermore, the coating, preferably of hydroxyapatite, may have BMPs adsorbed therein, to

further potentiate and/or accelerate induction of bone formation.

Further, according to the invention, there is provided a method of manufacturing an implant for bone replacement, which method includes providing a body of a suitable material, preferably hydroxyapatite or other ceramics, and size for implanting into a patient at a site where bone replacement and growth is required, and providing in the outer surface of the body, concavities which are of a shape and dimensions which induce or enhance the rate and/or amount of bone growth at the implantation site.

In such cases of solid implants made of metal such as titanium, then the method includes coating the implant with a biomaterial which will aid osteointegration. Such material is preferably bio-active, such as hydroxyapatite.

Manufacture of the implant may include profiling by either

(a) non-contact machining, such as laser machining, spark eroding, or

(b) contact machining via mechanical means, such as turning, drilling, milling, grinding, etc.

For example, in dentistry, a pure titanium or titanium alloy rod of suitable starting diameter can be turned down on a lathe to an appropriate diameter for implantation (usually either in the mandible or maxilla). Subsequently, the concavities in the outer surface can be provided by machining.

If the implant, when of metal, is to be used uncoated then, after machining, standard surface preparation techniques can be carried out, e.g. degreasing, cleaning, passivating, and sterilising. Surface preparations such as grit blasting prior to implantation and before cleaning can also be performed.

For applying a coating of a biomaterial to the implant, when made of metal such as titanium, to aid osteointegration, a number of physical and chemical techniques are available. These include, but are not limited to:

1. Biological deposition from simulated body fluid.
2. Adhesively bonding hydroxyapatite (HA) to the substrate.
3. Radiofrequency sputtering.
4. Pulsed laser deposition.
5. Hot isostatic pressing (HIPPING).
6. Reactive physical vapour deposition.

7. Slurry coating.
8. Electrophoretic deposition and sintering.
9. High velocity flame spraying.
10. Ion beam sputter deposition.
11. Magnetron sputtering.

Furthermore, after coating, a number of post-treatments can be carried out, for example,

1. Radiofrequency glow discharge treatment.
2. Vacuum heat treatment.
3. Ion implantation.

The currently preferred deposition techniques are based on thermal spray technology and, in particular, vacuum plasma spraying and air plasma spraying.

The invention is now described by way of the following non-limiting examples and with reference to the accompanying photographs and drawings, from which it will become apparent that the specific geometric configuration imparts to both porous and solid biomaterials the ability to induce the spontaneous initiation of bone formation.

In the Examples:

EXAMPLE 1 describes the spontaneous induction of bone within the porous spaces of the porous hydroxyapatite implant having specific geometric configurations,

after implantation in extraskeletal sites of a primate;

EXAMPLE 2 describes bone formation and growth into the porous hydroxyapatite implant having specific geometric configurations, after implantation in skeletal sites of a primate;

EXAMPLE 3 describes the rapid induction of bone formation within the porous spaces of the porous hydroxyapatite implant having specific geometric configurations, after implantation in extraskeletal sites of a primate after adsorption of BMPs onto the hydroxyapatite;

EXAMPLE 4 describes the rapid induction of bone formation and growth into the porous hydroxyapatite implant having specific geometric configurations, after implantation in skeletal sites of a primate after adsorption of BMPs onto the hydroxyapatite;

EXAMPLE 5 describes the spontaneous induction of bone only in specific geometric configurations created on the external surface of a solid implant of sintered hydroxyapatite when implanted in extraskeletal sites of a primate;

EXAMPLE 6 describes the osteointegration, bone formation and growth, and bone interlocking along the geometric configuration of a solid implant of titanium coated with hydroxyapatite and implanted in the edentulous jaw of a primate, and it extends also to describe the influence of the geometric configuration

on cell attachment and tissue matrix deposition in the specific geometric configurations created on the outer surface of the solid implant of titanium coated with hydroxyapatite when implanted in contact with muscular tissue of a primate;

In the photographs and drawings:

Figures 1 and 2 are photomacrographs of the porous sintered hydroxyapatite before implantation in a primate; and in particular, Figure 1 is a photomacrograph of the sintered porous hydroxyapatite prepared in disc configuration, suitable for implantation in circular calvarial defects of the baboon, with osteoinductive geometric configuration which form the framework of the hydroxyapatite, and Figure 2 is a scanning electron micrograph of the sintered porous hydroxyapatite illustrating the repetitive sequence of concavities according to the present invention.

Figures 3 to 6 are photomicrographs of sections prepared from sintered porous hydroxyapatite rods according to the invention, harvested from extraskeletal intramuscular sites (rectus abdominis) of a primate; in particular, Figure 3 shows a photomicrograph of histological section prepared from specimen of sintered porous hydroxyapatite rods harvested from intramuscular sites of the baboon on day 90 after implantation: bone (arrows) had spontaneously formed only along concavities of the hydroxyapatite substratum; Figure 4 shows a photomicrograph of histological section prepared from specimen of sintered porous hydroxyapatite rods harvested from intramuscular sites of the baboon on day 90 after

implantation: bone (arrows) had spontaneously formed only along concavities of the hydroxyapatite substratum; Figure 5 shows an extensive induction of bone after pre-treatment of the sintered porous hydroxyapatite with 5 mM hydrochloric acid; and Figure 6 shows a photomicrograph of a histological section prepared from a specimen of sintered porous hydroxyapatite in rod configuration pre-treated with BMPs and harvested from intramuscular sites of the baboon on day 30 after implantation: extensive bone induction and generation of bone marrow within the spheroidal porous spaces.

Figures 7 to 9 are photomicrographs of sections prepared from sintered porous hydroxyapatite discs according to the invention, harvested from the calvaria of a primate; in particular, Figure 7 shows a complete bone growth and penetration in the porous spaces of a sintered porous hydroxyapatite disc implanted in the calvaria of an adult baboon and harvested on day 90 after surgery. Arrows indicate the margins of the surgically created defects; Figure 8 shows a higher magnification showing bone growth within the spheroidal porous spaces (now occupied by newly formed bone) of the sintered hydroxyapatite implanted in the calvaria of an adult baboon and harvested on day 90 after surgery; and Figure 9 shows a photomicrograph of a histological section prepared from a specimen of sintered porous hydroxyapatite in disc configuration pre-treated with BMPs and harvested from the calvaria of the baboon on day 30 after implantation: extensive bone induction within the porous spaces of the sintered hydroxyapatite.

Figures 10 and 11 are photomicrographs of sections prepared from solid implants made of sintered hydroxyapatite with specific geometric configurations according to the invention; in particular, Figure 10 shows a photomicrograph of histological section prepared from specimen, of solid implants of sintered hydroxyapatite with osteoinductive geometric configurations of the present invention. Extensive bone formation and remodelling with generation of bone marrow (arrows) only in the concavities prepared on the outer surface of the solid hydroxyapatite. The specimens were harvested on day 90 after implantation in the rectus abdominis of an adult baboon; and Figure 11 shows photomicrograph of histological section prepared from specimen of solid implants of sintered hydroxyapatite with osteoinductive geometric configurations of the present invention. Extensive bone formation and remodelling with generation of bone marrow (arrows) only in the concavities prepared on the outer surface of the solid hydroxyapatite. The specimens were harvested on day 90 after implantation in the rectus abdominis of an adult baboon.

Figure 12 schematically illustrates a typical solid implant according to the invention;

Figure 13 illustrates a solid implant similar to that of Figure 12, made of titanium with hydroxyapatite coating (e.g. a dental implant) and geometric configurations at the outer surface according to the invention, just prior to implantation into a bony site of the primate; it shows a clinical photograph of the dental implant of the present invention just before surgical insertion in osseous site of

the baboon; the arrows indicate blood that has filled the concavities prepared on the outer surface of the implant.

Figures 14 and 15 are photomicrographs of sections prepared from solid implants made of titanium with hydroxyapatite coating and geometric configurations at the outer surface according to the invention and harvested from the jaw of a primate; Figure 14 is a photomicrograph of a histological section prepared from a dental implant prepared according to the invention and harvested on day 90 after surgical insertion in the jaw of the baboon. Bone formation and growth, and bone interlocking had formed along the concavities prepared on the outer surface of the solid implant; and Figure 15 is a higher magnification of previous section (Figure 14) highlighting bone formation and growth in direct apposition with the hydroxyapatite coating plasma sprayed over titanium (arrows). There was generation of bone marrow between the bone in contact with the implant and the surrounding bone of the jaw, but this cannot be seen in Figure 15; and

Figures 16 to 18 are photomacrographs of solid implants made of titanium coated with hydroxyapatite according to the invention illustrating preferential cell attachment and tissue matrix deposition within the specific geometric configuration of the implant when compared with standard implants without preparation of concavities at the outer surface of the implant; in particular, Figure 16 shows a scanning electron micrograph of the dental implant of the present invention showing cell attachment and tissue matrix deposition

preferentially within the concavities prepared at the outer surface of the implant; Figure 17 shows a scanning electron micrographs of the dental implant of the present invention showing cell attachment and tissue matrix deposition preferentially within the concavities prepared at the outer surface of the implant; and Figure 18 is a scanning electron micrograph of a standard dental implant without concavities on the outer surface of the implant showing lack of cell attachment and tissue matrix deposition.

The sintered porous hydroxyapatite biomaterial according to the invention was prepared in the following manner:

A slurry of well dispersed hydroxyapatite powder obtained from Merck S.A. under Product number 2196, was prepared in an alcohol/binder/plasticizer solution and a polyurethane foam was impregnated with this slurry. The composition of the binder/plasticizer mix was as follows: 90g polyethylene glycol #6000; 150g poly-vinyl butyral; 240g ethanol absolute; 600g trichloroethylene. The slurry was prepared using the

following batch composition: 70g hydroxyapatite; 50g ethanol absolute; 1g emphos PS-21A deflocculant; 36g binder/plasticizer mix. A commercial low porosity, low density polyurethane foam #30/14 (density/hardness) was used.

The foam was first immersed into the slurry and repeatedly compressed and expanded to ensure complete coverage of all pore walls. The excess slurry was then removed and the coated foam allowed to dry. The ceramic artefact was formed by heating the impregnated foam in stages to ensure the complete burn-out of all organic matter and finally sintering the hydroxyapatite using the following firing schedule: 90°C/h to 250°C, hold for 2 hours; 50°C/h to 650°C, hold for 5 hours; 200°C/h to 1200°C, holding for 2 hours; cooling at 200°C/h to ambient.

The artificial implants were shaped into discs and rods for implantation in the primate, but it should be understood that the implants can be of any other configuration with different dimensions for the required implant to fit the damaged or missing region of the bone.

The rods measured 20mm in length and 7mm in diameter and the discs measured 25mm in diameter and

4mm in thickness, and the pore sizes were in the region of 300μm to 2200μm.

Example 1:

To investigate the intrinsic osteoinductive activity of the sintered porous hydroxyapatite of the present invention, the rods were implanted intramuscularly (rectus abdominis) of primates (baboon, Papio ursinus) since only the extraskeletal implantation permits the histological investigation of bone formation by induction, avoiding the possible ambiguities of intraskeletal sites (where bone growth occurs from the viable bone interfaces of a bone defect). Before implantation, some of the rods were treated, just before implantation, with a liquid vehicle consisting of 5 mM hydrochloric acid. This treatment was achieved by wetting the sintered porous hydroxyapatite rods by pipetting 5 mM hydrochloric acid onto and into the hydroxyapatite substratum (preferably 300μl per 1000μg of sintered hydroxyapatite).

Example 2:

To investigate the overall effect of the sintered hydroxyapatite as biomaterial for bone repair and replacement, the discs were implanted in non-healing cranial defects, 25mm in diameter, surgically prepared in the calvaria of adult baboons.

Examples 3 and 4:

To investigate the efficacy of the sintered porous hydroxyapatite as carrier and delivery system for growth and morphogenetic factors, some implants were pre-treated by adsorbing BMPs, solubilized in 5 mM hydrochloric acid, onto the hydroxyapatite in both rod and disc configuration, which were then implanted in the rectus abdominis and the calvaria of the baboon, respectively.

Example 5:

To investigate the intrinsic osteoinductive activity of the solid implants for bone replacement of the present invention, sintered solid implants of hydroxyapatite in disc configuration (20mm in diameter and 4mm in thickness) with concavities prepared on the outer surface of the discs according to the invention, were implanted intramuscularly (rectus abdominis) of the baboon.

The rods, which were implanted intramuscularly, were harvested on day 30 and 90 respectively after implantation. The discs of sintered porous hydroxyapatite were also harvested on day 30 and 90 after implantation. Rods and discs with surrounding muscular tissue and calvaria bone, respectively, were processed for histological analysis, and serial

histological sections were prepared and stained using conventional methods.

The discs of solid sintered hydroxyapatite, which were implanted intramuscularly, were harvested on day 30 and 90 respectively after after implantation, and processed for histological analysis using conventional methods.

Intramuscular implants (rods):

The results showed that spontaneous bone formation occurred by day 30 and 90 after intramuscular implantation. Photomicrographs (as shown in Figures 3, 4 and 5) were taken from sections prepared from the sintered hydroxyapatite rods harvested from the intramuscular sites (rectus abdominis) of the baboon 90 days after implantation. The arrows in Figures 3 and 4 indicate bone which formed spontaneously along concavities of the hydroxyapatite substratum. Figure 5 shows extensive bone induction and generation of bone marrow after pre-treatment of the sintered porous hydroxyapatite with 5 mM hydrochloric acid.

Figure 6 shows the rapid and extensive bone induction and generation of bone marrow as early as 30 days after intramuscular implantation after adsorption of BMPs onto the hydroxyapatite.

From these photomicrographs it is evident that the bone formation occurred consistently in concavities of the porous surfaces of the sintered hydroxyapatite implant, but did not form on convexities, which observation supports the view that the geometric configuration of the implant is of critical importance for spontaneous bone induction to occur.

Moreover, enhanced osteoinduction is obtained by pre-treatment of the implants just before implantation by a liquid vehicle comprising 5 mM hydrochloric acid as shown in Figure 5.

It is important to note that this was achieved in the primate, and in a body site not in contact with viable bone, and underscores the critical importance of the geometry of the hydroxyapatite substratum for the spontaneous induction of bone formation.

Furthermore, rapid bone induction can be achieved (as shown in Figure 6) by prior adsorption of BMPs onto the hydroxyapatite, which observation indicates that the sintered porous hydroxyapatite implant of the present invention is efficaceous as carrier and as delivery system for the osteogenic activity of exogenous BMPs previously adsorbed onto the hydroxyapatite.

Calvarial implants (discs):

The results showed complete incorporation of the porous sintered hydroxyapatite implant within the cranial defects 90 days after implantation. Photomicrographs (see Figures 7 and 8) were taken from sections prepared from sintered porous hydroxyapatite discs harvested from the calvaria of the adult baboon, 90 days after surgery. The arrows in Figure 7 indicate the margins of the surgically created calvarial defects. Figure 8 is a higher magnification showing bone formation and growth within the spheroidal porous spaces (now occupied by newly formed bone) of the sintered porous hydroxyapatite.

Adsorption of BMPs onto the hydroxyapatite discs prior to insertion into calvarial defects of adult baboons showed extensive bone formation as early as 30 days after surgery, as shown in Figure 9.

Intramuscular implants (solid discs):

The results showed that spontaneous bone formation occurred by day 30 and 90 after intramuscular implantation of the solid hydroxyapatite implants of the present invention. Figures 10 and 11 show bone formation and generation of bone marrow (arrows) only within the concavities of solid hydroxyapatite discs harvested from intramuscular sites of the baboon on day 90 after implantation.

From these photomicrographs it is evident that the spontaneous induction of bone formation occurred only in the concavities prepared on the outer surface of the solid sintered hydroxyapatite implant, which observation indicates that the geometric configuration of the solid implant is also of critical importance for bone induction to occur, and that solid implants with an outer surface of hydroxyapatite with specific geometric configuration are endowed with intrinsic osteoinductive activity.

In Figure 12, reference numeral 10 generally indicates a solid implant according to the invention which comprises a body 12 manufactured from the following material: Ti-6Al-4V. The body comprises a rod of circular section with a diameter of 3.85mm, having a rounded head 14 at its forward end and integral formations 16 at its back end which formations 16 facilitate location of the implant body 12 in a desired site in a subject. The implant body 12 has an outer surface 18 which defines a plurality of concavities 20, each having a maximum diameter of about 1600μm, and a maximum depth of about 800μm. The concavities 20 are spaced apart a distance of about 800μm.

Figure 13 is a second embodiment of an implant according to the invention (just before surgical

implantation into a primate), which is similar in almost all respects to the implant 10 (as shown in Figure 12). The only difference is that the embodiment of Figure 13 is a plasma sprayed hydroxyapatite-coated implant. The coating thickness is in the region of about 60μm to about 80μm. Optionally bone morphogenetic proteins (BMPs) can be adsorbed onto the hydroxyapatite, thereby to achieve more rapid osteointegration by providing additional osteoinduction by exogenous applications of native or recombinant human BMPs.

The coating of hydroxyapatite was applied to the implant body 12 by air plasma spraying the hydroxyapatite coating (high crystallinity, low porosity, highly adherent) to the suitable prepared (see above) titanium substrate using conventional deposition techniques. A Metco 9MB plasma spray gun operating with an Ar/H_2 plasma at 35kW was used to deposit the coating. Prior to spraying with the hydroxyapatite (powder supplied by Metco - Plasma Technik, product AMDRY 6020), the titanium substrate was prepared for coating, i.e. roughened by grit blasting with alumina grit to produce the following surface profile:

$R_a > 3\mu m$, $R_t > 20\mu m$, $R_z > 15\mu m$.

Typical spray parameters are given below:

Plasma Gas:	Primary	Argon (5bar)
	Secondary	Hydrogen (5bar)
Gun Power		25-35kW
Powder Feed Rate		10-30g/min
Stand-Off Distance		60-100mm
Gun Velocity		100mm/min

Example 6:

To investigate the overall effect and efficacy of the solid implant of the present invention as biomaterial implant for bone replacement, solid implants of titanium with hydroxyapatite coating and with concavities prepared at the outer surface of the solid implant, were implanted in the edentulous jaw of the baboon.

The solid implants of titanium with hydroxyapatite coating, which were implanted in the edentulous jaw of the baboon, were harvested on day 30 and 90 after surgical implantation.

The results showed that bone formation and growth had occurred along the concavities of the solid implant of titanium coated with hydroxyapatite of the present invention (as shown in Figure 14). Figure 15 is a high power view showing bone formation and growth in direct apposition to the hydroxyapatite plasma

sprayed onto the titanium in the region of a concavity prepared on the outer surface of the solid implant (arrows). Bone formation and growth within the concavities enhances bone interlocking with the implant and superior fixation of the implant with surrounding viable bone, advantageous for implants for bone replacement during function.

Figures 16 and 17 are photomacrographs showing cell attachment and tissue matrix deposition preferentially occurring within the concavities prepared on the outer surface of the implant, which observation indicates the importance of the geometric configuration on tissue differentiation and tissue matrix deposition when compared to standard implants without the preparation of concavities, as shown in Figure 18.

It should be understood that although the abovementioned example of an implant according to the invention is one which is particularly suitable for dental applications, the invention should not be construed as being limited to dental implants. Indeed, application of the invention extends to craniofacial and orthopaedic use, as solid prosthetic implants for bone replacement (e.g. femoral and knee prostheses as in orthopaedic practice).

A major advantage of the invention, at least as exemplified, is the capability of the inventive implant with specific geometry to induce bone formation even in cases where the implant is not placed in direct contact with viable bone. It is of great importance to note that the invention provides biomaterial implants for orthopaedic, craniofacial and dental applications that are capable of spontaneous bone induction when implanted into the baboon, a primate that has bone physiology and remodelling comparable to man [9], the ultimate recipient of the biomaterial implant of the present invention.

Accordingly this invention provides a biomaterial for bone repair and replacement which is capable of spontaneous initiation of bone formation, i.e. a biomaterial implant with intrinsic osteogenic activity. It also provides sintered porous ceramic biomaterials and methods for their manufacture derived from synthetic hydroxyapatite particles as a starting material, capable of both osteoconduction and osteoinduction when implanted into a bone defect. Further, the invention provides sintered porous ceramic biomaterials for bone replacement having a defined porous macrostructure and a defined geometric configuration of the porous structure. Still further, the invention provides porous sintered ceramic biomaterials which provide an optimal substratum for

adsorption of growth and morphogenetic factors, including, but not limited to, BMPs.

The sintered hydroxyapatite of the present invention has the following advantages over the hydroxyapatite derived via hydrothermal exchange from naturally occurring coral. The sintered hydroxyapatite of the invention (a) is pure highly crystalline hydroxyapatite, (b) the pore sizes and uniformity thereof in an implant comprising such pure hydroxyapatite, is controllable, and (c) the shapes of the pores are beneficially more rounded, being substantially spherical in configuration. In contrast, the hydroxyapatite derived from the naturally occurring coral material (a) is not pure hydroxyapatite (generally comprising about 10% of a phosphate impurity), (b) does not have controllable pore sizes, and (c) comprises pores in the form of channels which extend along substantially the entire width or length of an implant made from the conventional material. Furthermore, the osteoinductive geometric configuration prepared on the outer surface of the implant of both porous and solid implants of sintered hydroxyapatite has the advantage of initiating the spontaneous induction of bone formation along the concavities on the outer surface of the implant, thereby enhancing the osteointegration with the surrounding viable bone, when the implant is

placed into a bone defect of the primate. It is important to point out that, in coral-derived hydroxyapatite, bone is never observed on the outer surface of the implant [5,7].

It will therefore be appreciated that a major advantage of the invention, at least as exemplified, is the capability of the inventive implant with specific geometry to induce bone formation even in cases where the implant is not placed in direct contact with viable bone. Another advantage of the invention is that porous hydroxyapatite obtained after sintering is an optimum substratum for adsorption of BMPs additionally potentiating the osteogenic properties of the implant.

The preferred method of complexing growth and morphogenetic factors onto the porous substratum of the sintered hydroxyapatite biomaterial of the invention, is as follows:

(a) the biomaterial is placed in a chromatography column,

(b) the BMPs are dissolved or suspended in a suitable fluid vehicle therefor,

(c) the dissolved or suspended BMPs are introduced into the column at a controlled rate, and

(d) the BMPs are contacted with the biomaterial of the invention in the column so that the BMPs are adsorbed onto the biomaterial.

Details of such a method of adsorption are available from South African Patent No. 92/3608.

Instead, BMPs can be manually loaded onto the sintered hydroxyapatite biomaterial according to the invention, by means of a pipette containing the BMPs dissolved or suspended in a suitable fluid vehicle therefor preferably 5 mM hydrochloric acid.

FIGURE LEGENDS

FIGURE 1:

Photomacrograph of the sintered porous hydroxyapatite prepared in disc configuration, suitable for implantation in circular calvarial defects of the baboon, with osteoinductive geometric configuration which form the framework of the hydroxyapatite.

FIGURE 2:

Scanning electron micrograph of the sintered porous hydroxyapatite illustrating the repetitive sequence of concavities according to the present invention.

FIGURES 3 and 4:

Photomicrographs of histological sections prepared from specimens of sintered porous hydroxyapatite rods harvested from intramuscular sites of the baboon on day 90 after implantation: bone (arrows) had spontaneously formed only along concavities of the hydroxyapatite substratum.

FIGURE 5:

Extensive induction of bone after pre-treatment of the sintered porous hydroxyapatite with 5 mM hydrochloric acid.

FIGURE 6:

Photomicrograph of a histological section prepared from a specimen of sintered porous hydroxyapatite in rod configuration pre-treated with BMPs and harvested from intramuscular sites of the baboon on day 30 after

implantation: extensive bone induction and generation of bone marrow within the spheroidal porous spaces.

FIGURE 7:

Complete bone growth and penetration in the porous spaces of a sintered porous hydroxyapatite disc implanted in the calvaria of an adult baboon and harvested on day 90 after surgery. Arrows indicate the margins of the surgically created defects.

FIGURE 8:

Higher magnification showing bone growth within the spheroidal porous spaces (now occupied by newly formed bone) of the sintered hydroxyapatite implanted in the calvaria of an adult baboon and harvested on day 90 after surgery.

FIGURE 9:

Photomicrograph of a histological section prepared from a specimen of sintered porous hydroxyapatite in disc configuration pre-treated with BMPs and harvested from the calvaria of the baboon on day 30 after implantation: extensive bone induction within the porous spaces of the sintered hydroxyapatite.

FIGURES 10 and 11:

Photomicrographs of histological sections prepared from specimens of solid implants of sintered hydroxyapatite with osteoinductive geometric configurations of the present invention. Extensive bone formation and remodelling with generation of bone marrow (arrows) only in the concavities prepared on

the outer surface of the solid hydroxyapatite. The specimens were harvested on day 90 after implantation in the rectus abdominis of an adult baboon.

FIGURE 12:

Schematic illustration of a solid implant with specific geometric configurations according to the invention.

FIGURE 13:

Clinical photograph of the dental implant of the present invention just before surgical insertion in osseous site of the baboon. Arrows indicate blood that has filled the concavities prepared on the outer surface of the implant.

FIGURE 14:

Photomicrograph of a histological section prepared from a dental implant prepared according to the invention and harvested on day 90 after surgical insertion in the jaw of the baboon. Bone formation and growth, and bone interlocking had formed along the concavities prepared on the outer surface of the solid implant.

FIGURE 15:

Higher magnification of previous section (Figure 14) highlighting bone formation and growth in direct apposition with the hydroxyapatite coating plasma sprayed over titanium (arrows). There was generation of bone marrow between the bone in contact with the

implant and the surrounding bone of the jaw, but this cannot be seen in Figure 15.

FIGURES 16 and 17:

Scanning electron micrographs of the dental implant of the present invention showing cell attachment and tissue matrix deposition preferentially within the concavities prepared at the outer surface of the implant.

FIGURE 18:

Scanning electron micrograph of a standard dental implant without concavities on the outer surface of the implant showing lack of cell attachment and tissue matrix deposition.

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Claims:

1. A biomaterial which can be used for at least part of a bone implant to be implanted into a subject at a site where bone growth is required, which biomaterial has an outer surface which defines dents with shapes and dimensions which impart to the biomaterial the ability to induce or enhance the rate and/or amount of bone growth at the site.

2. A biomaterial as claimed in claim 1 wherein the concavities defined by the outer surface of the biomaterial have a diameter of about 200μm to about 3000μm, and a depth of about 200μm to about 3000μm.

3. A biomaterial as claimed in claim 1 or 2, which has a specific porous configuration, and its inner geometry is characterised by pores which are substantially spherical in shape, and are in the region of 300μm to 2000μm in diameter.

4. A biomaterial as claimed in any one of claims 1 to 3, wherein the regions of the outer surface of the biomaterial at the respective peripheries of the concavities are rounded, and the concavities are spaced apart from one another by a distance of about 500μm to about 3000μm.

5. A biomaterial as claimed in any one of the previous claims, wherein the concavities have a diameter of about 1600μm and a depth of about 800μm, and the concavities are spaced apart from one another by a distance of about 2000μm.

6. A biomaterial as claimed in any one of claims 1 to 5, which is of hydroxyapatite.

7. A biomaterial as claimed in any of the preceding claims, which is of sintered hydroxyapatite which has been prepared by

selecting or manufacturing stearic acid beads of about 300 to about 3000μm,

mixing hydroxyapatite powder with the stearic acid beads,

forming a compact of the resulting mixture, and

sintering the compact.

8. A biomaterial as claimed in any one of claims 1 to 6, which is of sintered hydroxyapatite which has been prepared by

selecting an organic resin with a three-dimensional network structure which is a negative replica of the biomaterial,

impregnating a slurry of hydroxyapatite powder into the organic resin,

drying the slurry, and

removing the organic resin.

9. A bone implant for implanting into a subject at a site where bone growth is required, said implant comprising a body with an outer surface which defines dents which are selected, according to their shape and dimensions, for their ability to induce or to enhance the rate and/or amount of bone growth at the site.

10. A bone implant as claim in claim 9, wherein the dents are in the form of concavities having a diameter of about 200μm to about 3000μm and a depth of about 200μm to about 3000μm.

11. A bone implant as claimed in claim 10, wherein the regions of the outer surface of the implant at the respective peripheries of the concavities, are rounded, and the concavities are spaced apart from one another by a distance of about 500μm to about 3000μm.

12. A bone implant as claimed in claim 10 or claim 11, wherein the concavities have a diameter of about 1600μm and a depth of about 800μm, and the concavities are spaced apart from one another by a distance of about 2000μm.

13. A bone implant as claimed in any one of claims 9 to 12, which comprises a biomaterial having a porous

configuration with an inner geometry characterised by pores which are of shapes and dimensions which impart to the biomaterial the ability to induce or enhance the rate and/or amount of bone growth at the site.

14. A bone implant as claimed in claim 13, wherein the pores are in the region of 300μm to 3000μm in diameter.

15. A bone implant as claimed in claim 13 or claim 14, wherein the outer surface of the biomaterial has been treated with a liquid etchant.

16. A bone implant as claimed in any one of claims 13 to 15, which has native or recombinant human bone morphogenetic proteins (BMPs) adsorbed therein.

17. A bone implant as claimed in any one of claims 9 to 16, which is a dental implant.

18. A method of preparing a biomaterial which can be used for at least part of a bone implant to be implanted into a subject at a site where bone growth is required, which includes

selecting or manufacturing stearic acid beads which are complementary, in respect of their shapes and dimensions, to concavities which impart to the

biomaterial the ability to induce or enhance the rate and/or amount of bone growth at the site,

mixing a ceramic powder with the stearic acid beads,

forming a compact of the mixture of the powder and the beads, and

sintering the compact.

19. A method as claimed in claim 18, wherein the stearic acid beads have a diameter of about 200μm to about 3000μm.

20. A method of preparing a biomaterial which can be used for at least part of a bone implant to be implanted into a subject at a site where bone growth is required, which includes

selecting an organic resin with a three-dimensional network structure which is a negative replica of a biomaterial having pores with shapes and dimensions which impart to the biomaterial the ability to induce or enhance the rate and/or amount of both growth at the site,

impregnating a slurry of a ceramic powder into the organic resin,

drying the slurry, and

removing the organic resin.

21. A method as claimed in claim 20, wherein the organic resin is a negative replica of a biomaterial having pores with a diameter of about 200µmm to about 3000µm.

22. A method of manufacturing a bone implant, which method includes providing a body of a suitable material and size for implanting in a subject at a site where bone growth is required, and providing in an outer surface of the body, concavities having a diameter of about 200µm to about 3000µm and a depth of about 200µm to about 3000µm.

23. A method of manufacturing a bone implant as claimed in claim 22, for use in dentistry, and wherein the body is of pure titanium or of a titanium alloy.

24. A method of manufacturing a bone implant as claimed in claim 22 or claim 23, which includes coating the body with a biomaterial having a three-dimensional porous structure which defines concavities of about 200µm to 3000µm in diameter and about 200µm to 3000µm in depth.

25. A method of inducing or enhancing the rate and/or amount of bone growth in a subject, in a site where bone growth is desired, which method includes

selecting a bone implant having an appropriate overall shape and size for accommodation in the site, and comprising a body with an outer surface which defines dents which are selected, according to their shape and dimensions for their ability to induce or to enhance the rate and/or amount of bone growth at the site; and

placing the implant into the subject in the site where bone growth is desired.

26. A method as claimed in claim 25 wherein the dents are in the form of concavities have a diameter in the region of about 200μm to about 3000μm and a depth of about 200μm to about 3000μm.

27. A method as claimed in claim 25, wherein at least an outer portion of the bone implant comprises an hydroxyapatite biomaterial, and the method includes treating the surface of the implant with liquid etchants before placing it into the subject.

28. A method as claimed in any one of claims 25 to 27, wherein at least the outer surface of the bone implant comprises a coating of hydroxyapatite, and the method includes adsorbing bone morphogenetic proteins onto the hydroxyapatite coating before placing it into the subject.

29. A new biomaterial, substantially as herein described.

30. A new bone implant, substantially as herein described.

31. A new method of preparing a biomaterial, substantially as herein described.

32. A new method of manufacturing a bone implant, substantially as herein described.

33. A new method of inducing, or enhancing the rate and/or amount of bone growth, substantially as herein described.

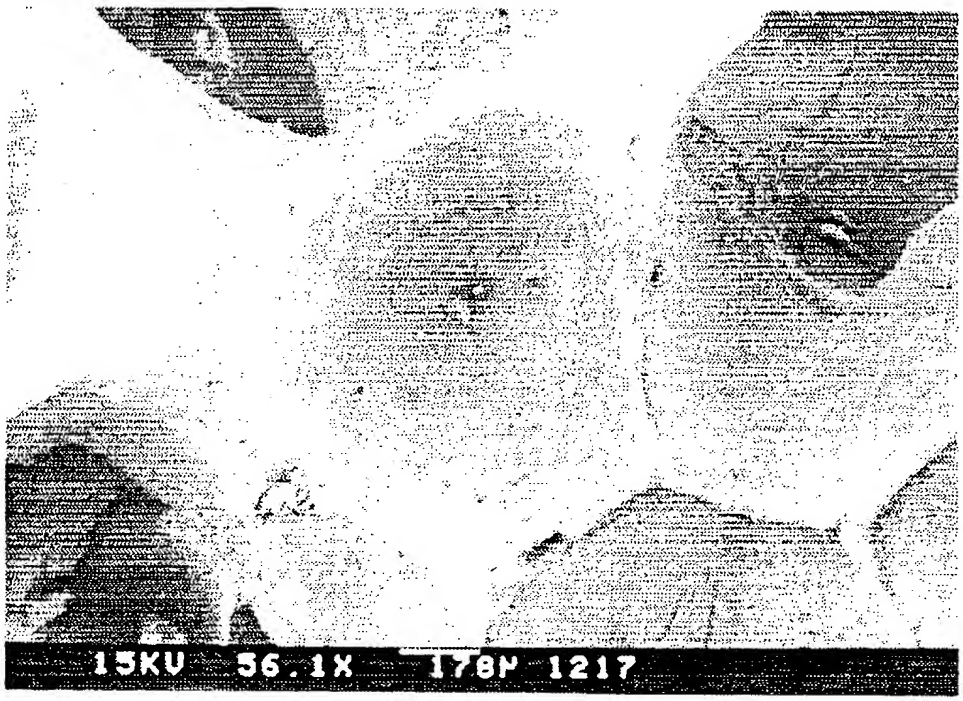

Fig. 1

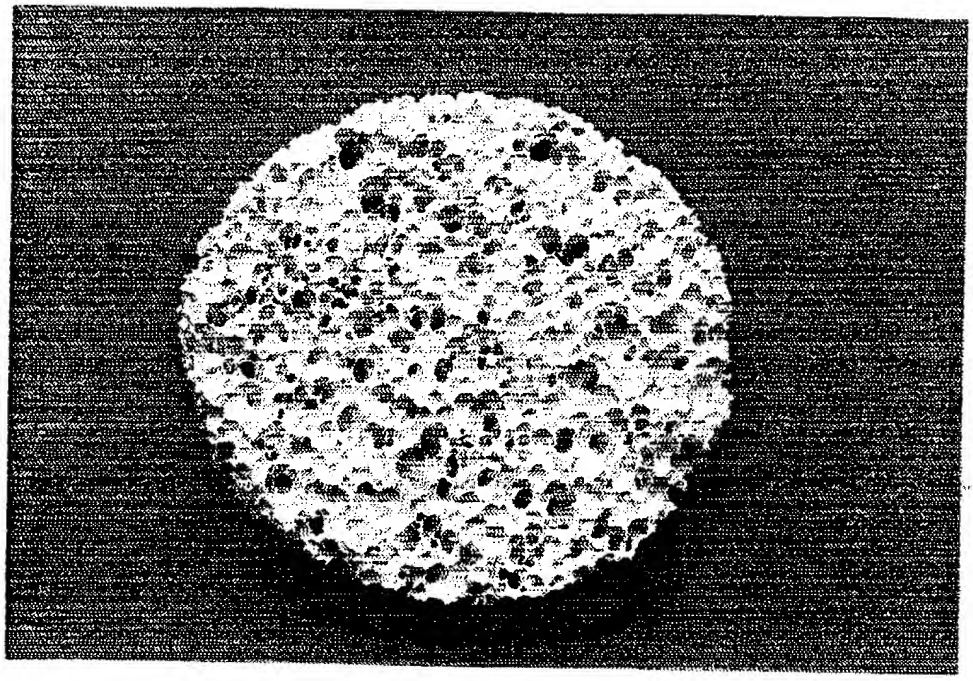

Fig. 2

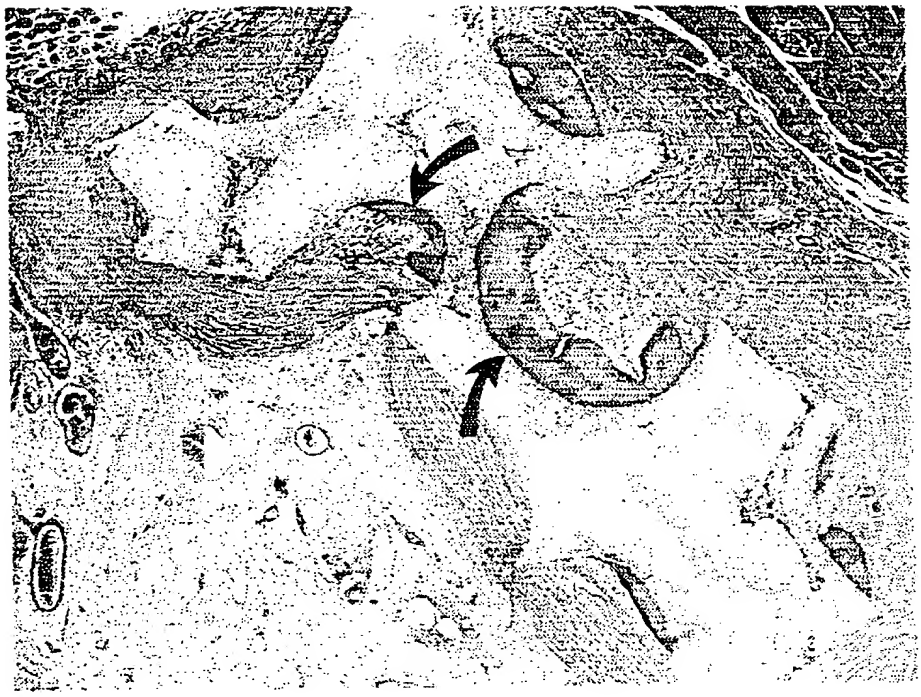

Fig. 3

Fig. 4

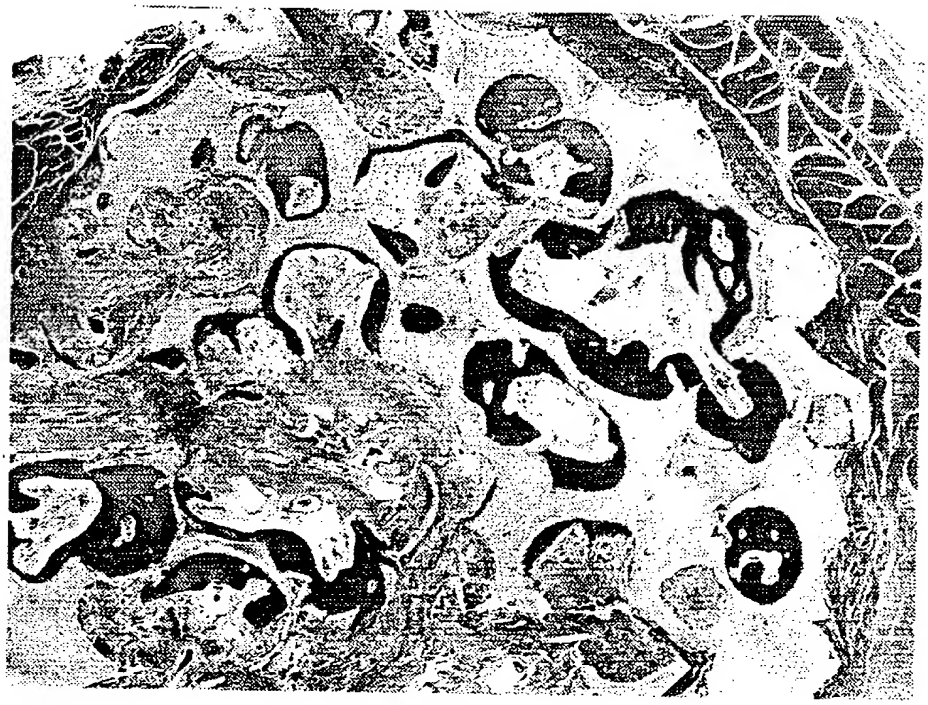

Fig. 5

Fig. 6

Fig. 7

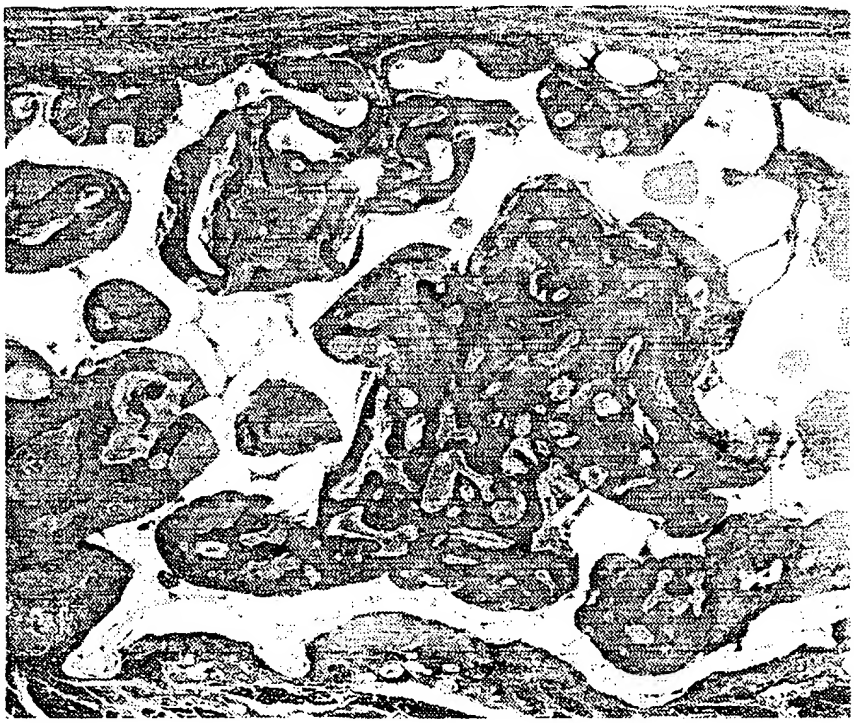

Fig. 8

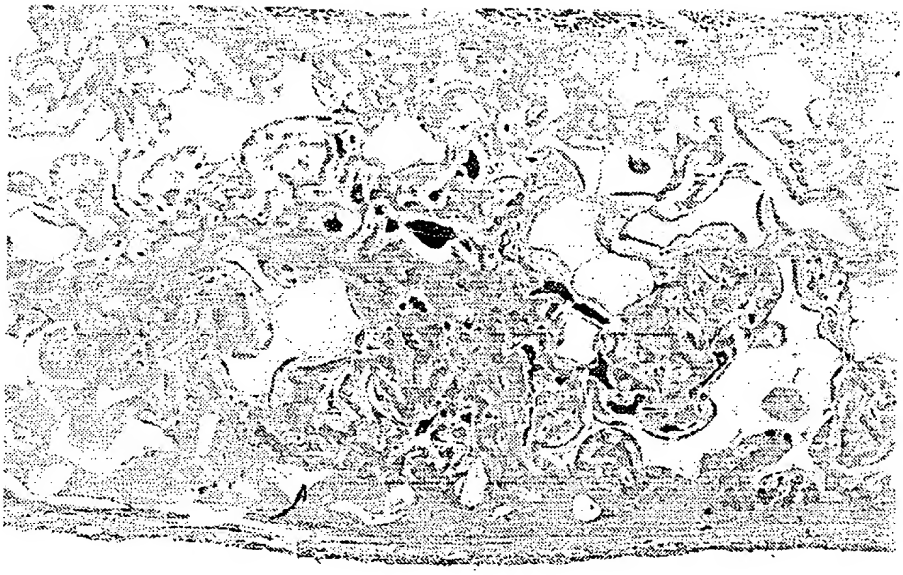

Fig. 9

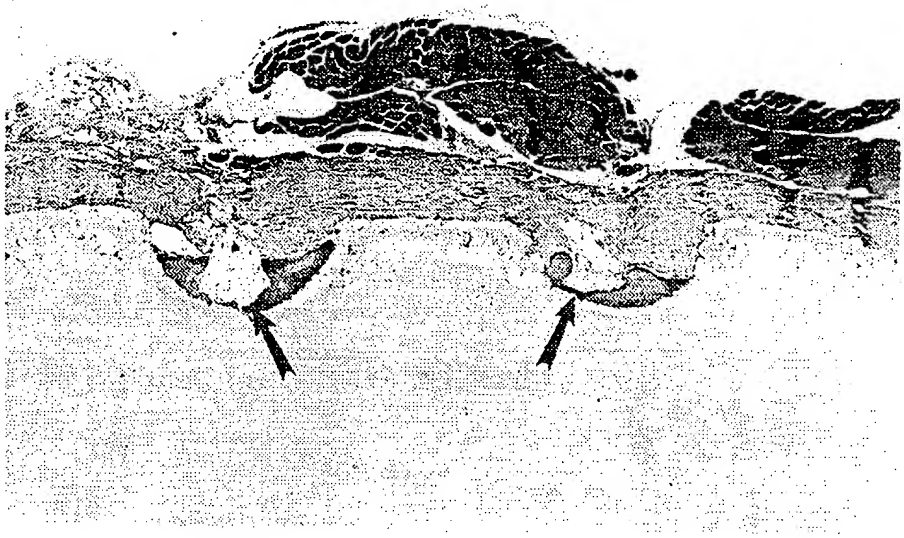

Fig. 10

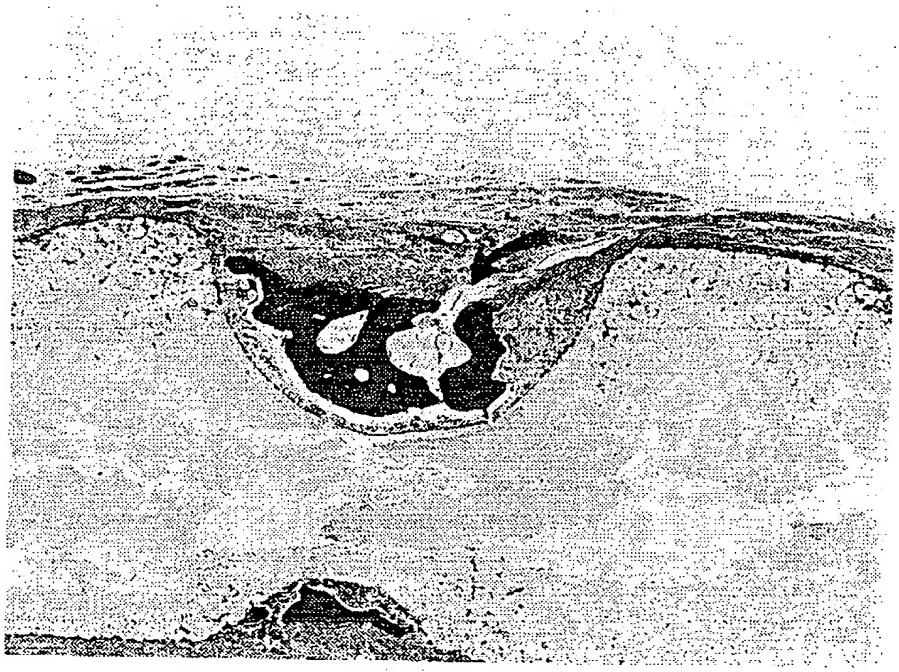

Fig. 11

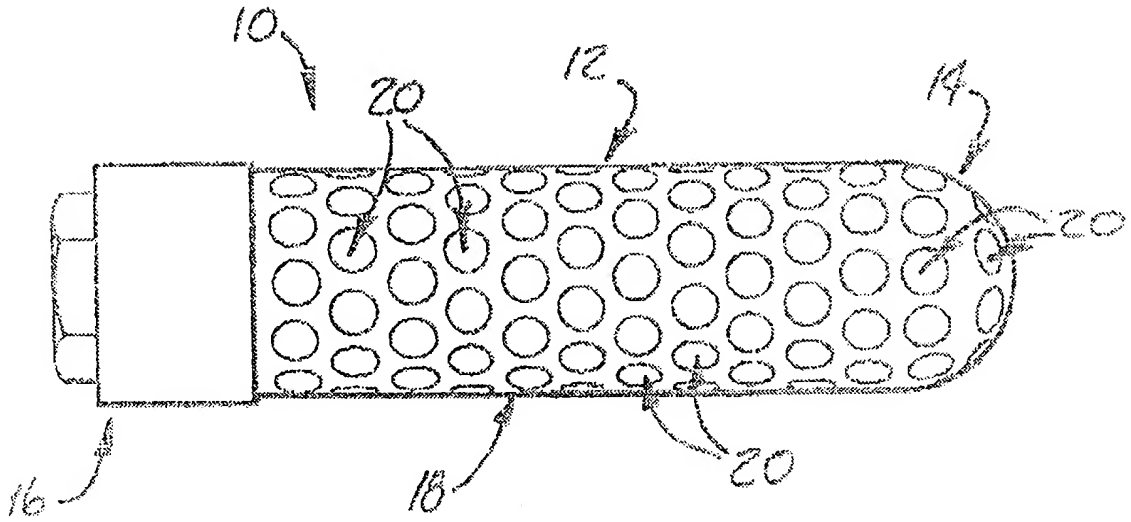

FIG 12

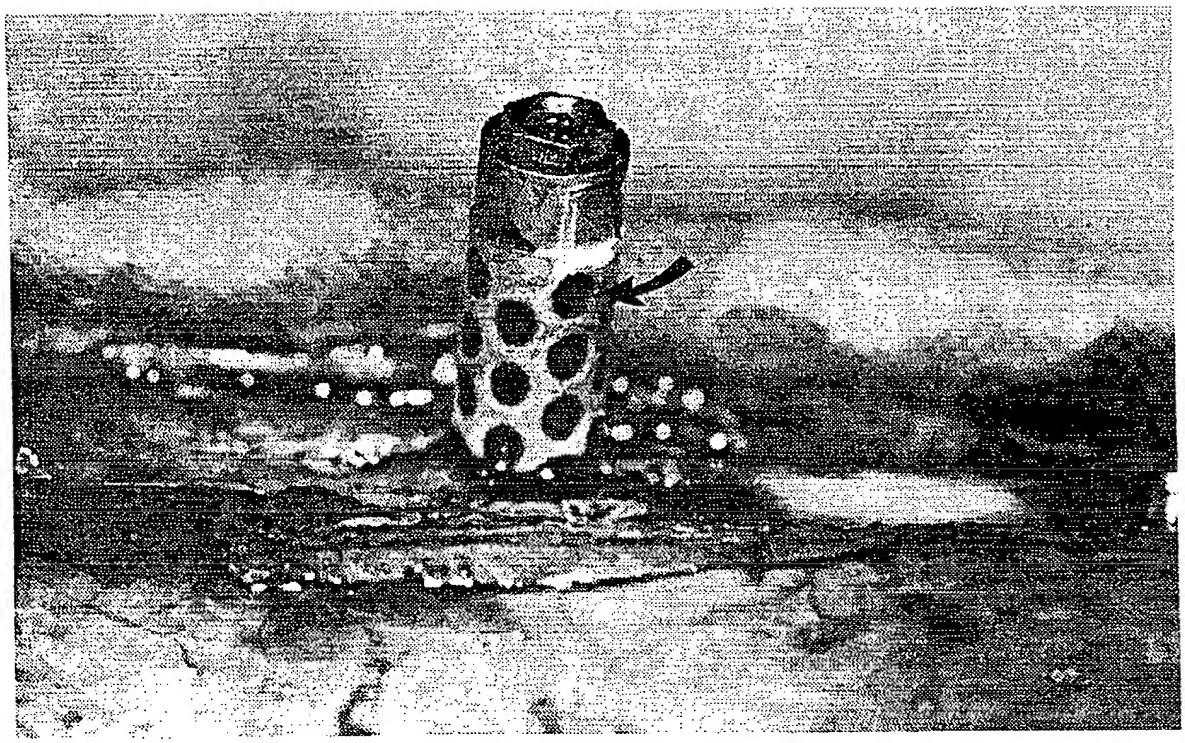

Fig. 13

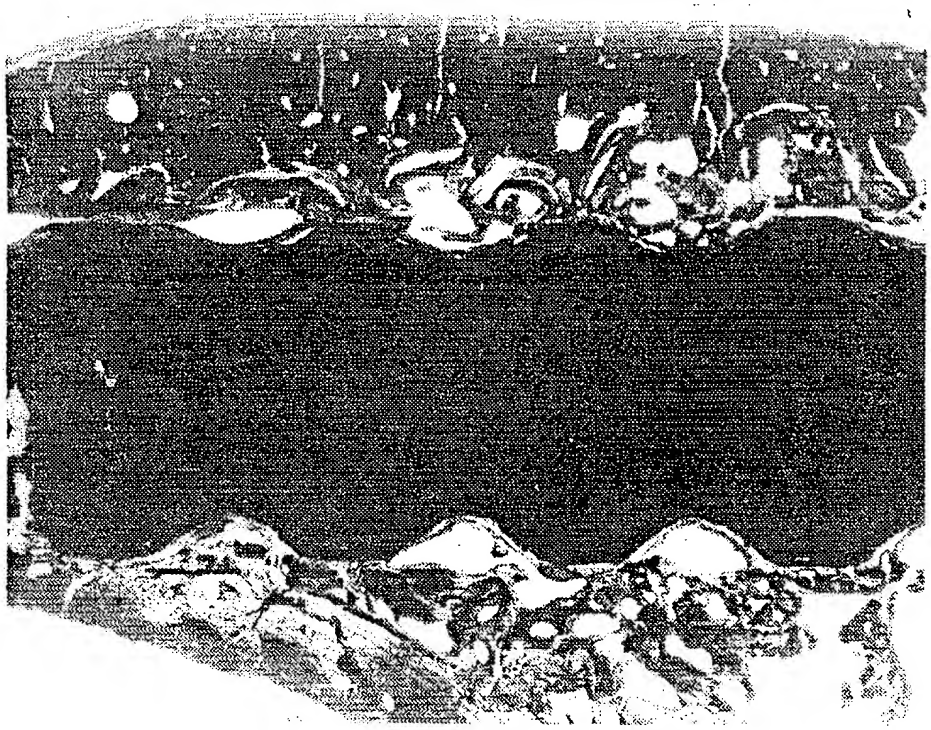

Fig. 14

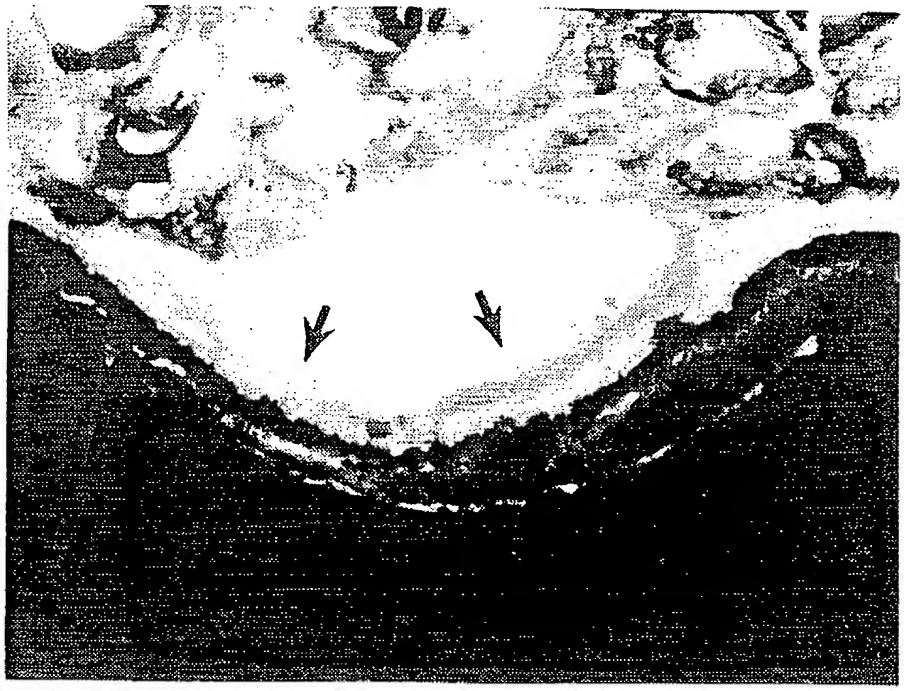

Fig. 15

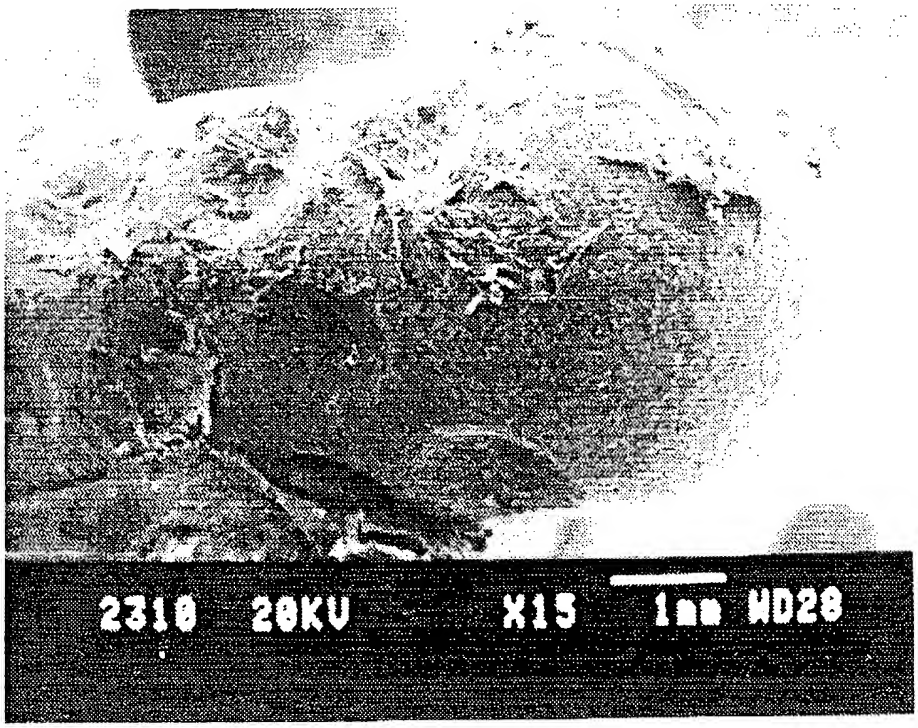

Fig. 16

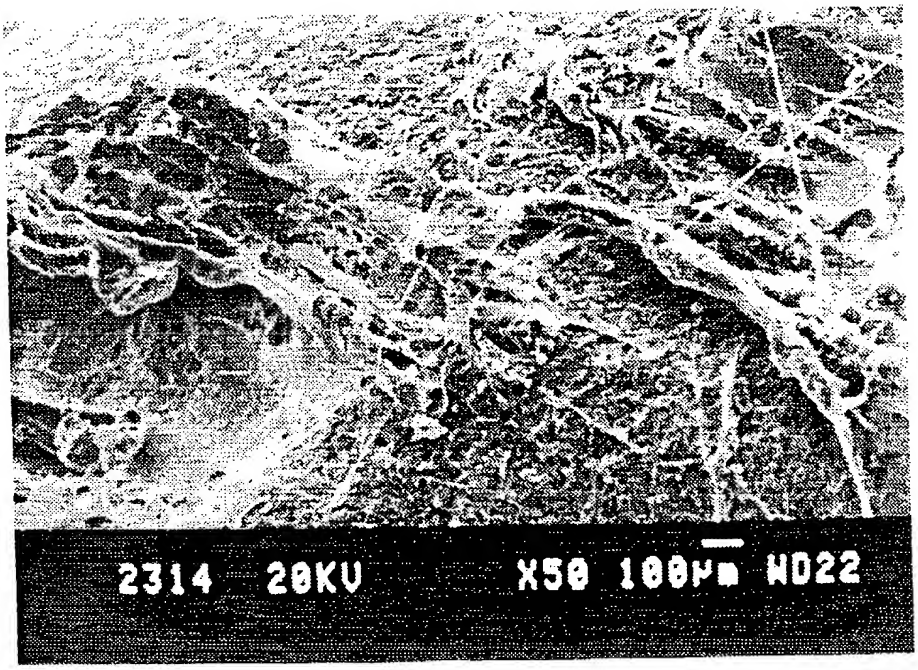

Fig. 17

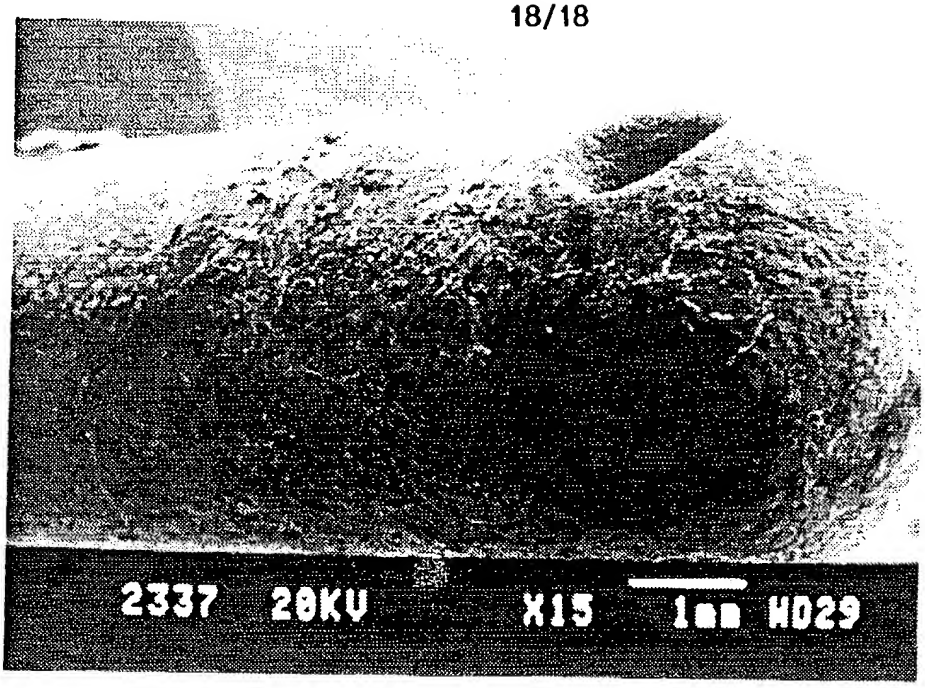

Fig. 18

INTERNATIONAL SEARCH REPORT

onal Application No
T/NL 95/00181

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00 A61F2/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X,P	WO,A,94 28827 (DEPUY INT LTD ;WROBLEWSKI BOGUSLAW MICHAEL (GB)) 22 December 1994 see page 4, paragraph 4 - page 6, paragraph 3	1-5,9-14
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Y	see page 3, line 8 - line 19 see page 4, line 36 - page 5, line 24 see page 6, line 29 - page 8, line 7 see page 13, line 33 - page 15, line 4 see page 16, line 8 - page 17, line 21	7,16,18
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 September 1995	11.10.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Cousins-Van Steen, G

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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